

Serial No. 10/789,956  
Docket No. SHE0081.00REMARKSRECEIVED  
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AUG 23 2006

**I. Introductory Comments**

In the Office Action under reply, the Examiner has maintained the following rejections, as follows: under 35 U.S.C. §103(a) as allegedly being unpatentable over Minamino et al. (U.S. Patent No. 6,037,452) in view of Greenwald (U.S. Patent No. 5,298,643) (claims 1, 3-4 and 8-11); and under 35 U.S.C. §103(a) as allegedly being unpatentable over Röstin et al. [Röstin et al. (2000) *Bioconjugate Chem.* 11:387-396] in view of Greenwald (U.S. Patent No. 5,298,643) (claims 1, 14 and 16);

Further, in the Office Action under reply, the Examiner has issued the following new objections/rejections, as follows: under 35 U.S.C. §112, second paragraph, for reasons of alleged indefiniteness (claims 26-30); under 35 U.S.C. §103(a) as allegedly being unpatentable over Minamino et al. (U.S. Patent No. 6,037,452) in view of Davis et al. (U.S. Patent No. 4,179,337) (claims 1-4, 8-9, 14-15, 17-20, 22-23 and 62); under 35 U.S.C. §103(a) as allegedly being unpatentable over Minamino et al. (U.S. Patent No. 6,037,452) and Davis et al. (U.S. Patent No. 4,179,337) as applied to claims 1-4, 8-9, 14-15, 17-20, 22-23 and 62, and further in view of Patton et al. (U.S. Patent No. 2003/0118510) (claims 1-10, 12-13, 21, 24-28 and 62); and under 35 U.S.C. §103(a) as allegedly being unpatentable over Minamino et al. (U.S. Patent No. 6,037,452) and Davis et al. (U.S. Patent No. 4,179,337) as applied to claims 1-4, 8-9, 14-15, 17-20, 22-23 and 62, and further in view of Bentley et al. (U.S. Patent No. 2003/0161791) (claims 1, 29 and 30).

The rejections are traversed for reasons provided below.

**II. Amendments to the Claims**

Claims 1-30 and 62 were previously pending (as claims 31-61 were previously withdrawn without prejudice). As provided in Section I above, claims 1 and 26-30 have been amended. No new claims have been added.

Support for the changes to the claims is identified below. Additional support other than that identified below may exist in the originally filed application for one or more changes to the claims.

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Claim 1 has been amended to recite that the conjugate is a "1-mer, 2-mer or 3-mer."

Support for the change can be found at Paragraph 0125.

Claims 26-30 have been amended to recited the phrase "the one, two or three water-soluble polymers are covalently attached by" in order to increase the clarity of the claim. Support for the phrase is found in pending claim 1.

As support for the change is found in the application as filed, no new matter is introduced by the entry of the above-identified change. The changes to claims 1 and 26-30 are made for clarification purposes only should not be interpreted as acquiescence in any claim rejection.

### III. The First Rejection Under 35 U.S.C. §103(a)

The Examiner has maintained the rejection of claims 1, 3-4 and 8-11 under 35 U.S.C. §103(a) as allegedly being unpatentable over Minamino et al. (U.S. Patent No. 6,037,452) in view of Greenwald (U.S. Patent No. 5,298,643).

The rejection is respectfully traversed in view of the following remarks.

The standard for establishing a *prima facie* case of obviousness was provided in a previous response by Applicants.

In support for maintaining this obviousness rejection over Applicants' previous argument, the Examiner explained that the

"rejected claims depend from an independent base claim that uses the transitional phrase comprising with regards to the number of water-soluble polymers covalently attached to [the] Factor VIII Moiety; therefore there is no upper limit to the number of water-soluble polymers attached to the Factor VIII moiety.

See February 23, 2006, Office Action, page 3 (emphasis in original).

Thus, the Examiner takes the position that the claim in question encompasses conjugates having "1, 2, 3, 4, 5, 6, 7, 8 or more water-soluble polymers individually attached to a Factor VIII moiety." The Examiner adopts this position even though the "ordinary and customary" meaning of the conjunction "or" makes clear that *only* one, two *or* three water-soluble polymers are covalently attached to the Factor VIII moiety.

In any event, and in an effort to expedite prosecution of the present application, Applicants have amended claim 1 to recite that the conjugate is a "1-mer, 2-mer or 3-mer." As indicated in Paragraph 0125 of the present specification, the terms 1-mer, 2-mer, 3-mer and so

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forth refer to the "differently numbered polymer-to-Factor VIII moiety ratios ... wherein '1-mer' indicates 1 polymer to Factor VIII moiety, '2-mer' indicates two polymers to Factor VIII moiety and so on." See Paragraph 0125. By amending the claims in this way, it is abundantly clear that the Applicants claims do have "an upper limit to the number of water-soluble polymers attached to the Factor VIII moiety and do not encompass Factor VIII moiety-polymer conjugates having four or more water-soluble polymers attached to the Factor VIII moiety. Thus, Minamino et al. -- which describes relatively high polymer-to-active ratios -- neither teaches nor suggests water-soluble polymer-Factor VIII moiety 1-mer conjugates, 2-mer conjugates or 3-mer conjugates, much less conjugates wherein such conjugates include a water-soluble polymer having a nominal average molecular weight from 6,000 Daltons to 150,000 Daltons.

As indicated previously, Greenwald describes reacting aryl imidate activated polyalkylene oxide with  $\epsilon$ -NH<sub>2</sub> moieties of lysines and that "the degree of conjugation is limited only by the number of  $\epsilon$ -NH<sub>2</sub> moieties of lysines." See Greenwald at column 8, lines 4-15. Again, given the 158 amine-containing lysine residues in native Factor VIII (see paragraph 0107), it is clear that Greenwald describes conjugates wherein each conjugate has a relatively larger number of polymers attached to a protein or polypeptide. Thus, Greenwald neither discloses or suggests 1-mer conjugates, 2-mer conjugates or 3-mer conjugates of water-soluble polymers covalently attached to a Factor VIII moiety, wherein each water-soluble polymer has a nominal average molecular weight in the range of from 6,000 Daltons to 150,000 Daltons.

Consequently, as neither Minamino et al. nor Greenwald teaches or suggests all the claim elements, the third prong of *prima facie* obviousness fails to be satisfied. As a result, the obviousness rejection of claims 1, 3-4 and 8-11 under 35 U.S.C. §103(a) is unsustainable. Reconsideration and withdrawal of the rejection for at least the reasons provided above is respectfully requested.

#### IV. The Second Rejection Under 35 U.S.C. §103(a)

The Examiner has maintained the rejection of claims 1, 14 and 16 under 35 U.S.C. §103(a) as allegedly being unpatentable over Röstin et al. [Röstin et al. (2000) *Bioconjugate Chem.* 11:387-396] in view of Greenwald (U.S. Patent No. 5,298,643).

The rejection is respectfully traversed in view of the following remarks.

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The standard for establishing a *prima facie* case of obviousness was provided in a previous response by Applicants.

As pointed out above in Section III, Minamino et al. neither teaches nor suggests water-soluble polymer-Factor VIII moiety 1-mer conjugates, 2-mer conjugates or 3-mer conjugates, much less conjugates wherein the water-soluble polymer has a nominal average molecular weight from 6,000 Daltons to 150,000 Daltons.

Röstin et al. describes the preparation of several compositions of conjugates. Each of Röstin et al.'s described compositions of conjugates is prepared using polymers having molecular weights of 3,000 Daltons or 5,000 Daltons. Thus, Röstin et al. neither discloses nor suggests 1-mer conjugates, 2-mer conjugates or 3-mer conjugates of water-soluble polymers covalently attached to a Factor VIII moiety, wherein each water-soluble polymer has a nominal average molecular weight in the range of from 6,000 Daltons to 150,000 Daltons.

Greenwald, which was discussed in Section III, does not cure the deficiencies of Röstin et al. For example, the feature of 1-mer conjugates, 2-mer conjugates or 3-mer conjugates of water-soluble polymers covalently attached to a Factor VIII moiety, wherein each water-soluble polymer has a nominal average molecular weight in the range of from 6,000 Daltons to 150,000 Daltons is neither disclosed nor suggested in Greenwald.

Consequently, as neither Röstin et al. nor Greenwald teach or suggest all the claim elements, the third prong of *prima facie* obviousness fails to be satisfied. As a result, the obviousness rejection of claims 1, 14 and 16 under 35 U.S.C. §103(a) is unsustainable. Reconsideration and withdrawal of the rejection for at least the reasons provided above is respectfully requested.

#### **V. The 35 U.S.C. §112, Second Paragraph, Rejection**

The Examiner has rejected claims 26-30 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Applicants have amended claims 26-30 to make it clear that the linkage recited in each of these claims is between the water-soluble polymer and Factor VIII moiety residues.

Consequently, reconsideration and removal of the rejection for at least this reason is respectfully requested.

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#### **VI. The Third Rejection Under 35 U.S.C. §103(a)**

The Examiner has rejected claims 1-4, 8-9, 14-15, 17-20, 22-23 and 62 under 35 U.S.C. §103(a) as allegedly being unpatentable over Minamino et al. (U.S. Patent No. 6,037,452) in view of Davis et al. (U.S. Patent No. 4,179,337).

The rejection is respectfully traversed in view of the following remarks.

The standard for establishing a *prima facie* case of obviousness was provided in a previous response by Applicants.

As pointed out in Section III, Minamino et al. neither teaches nor suggests water-soluble polymer-Factor VIII moiety 1-mer conjugates, 2-mer conjugates or 3-mer conjugates, much less conjugates wherein the water-soluble polymer has a nominal average molecular weight from 6,000 Daltons to 150,000 Daltons.

Davis et al. describes utilization of "between 10 and 100, suitably between 15 to 50 moles of polymer per mole of polypeptide." See Davis et al. at column 3, lines 10-13. Further, Davis et al. describes compositions comprising between 10 and 100 polymer moieties per molecule of insulin (Davis et al., claim 5) and enzyme (Davis et al., claim 19). Thus, like Minamino et al., Davis et al. neither teaches nor suggests water-soluble polymer-Factor VIII moiety 1-mer conjugates, 2-mer conjugates or 3-mer conjugates.

Consequently, as neither Minamino et al. nor Davis et al. teach or suggest all the claim elements, the third prong of *prima facie* obviousness fails to be satisfied. As a result, the obviousness rejection of claims 1-4, 8-9, 14-15, 17-20, 22-23 and 62 under 35 U.S.C. §103(a) is unsustainable. Reconsideration and withdrawal of the rejection for at least the reasons provided above is respectfully requested.

#### **VII. The Fourth Rejection Under 35 U.S.C. §103(a)**

The Examiner has rejected claims 1-10, 12-13, 21, 24-28 and 62 under 35 U.S.C. §103(a) as allegedly being unpatentable over Minamino et al. (U.S. Patent No. 6,037,452) and Davis et al. (U.S. Patent No. 4,179,337) as applied to claims 1-4, 8-9, 14-15, 17-20, 22-23 and 62, and further in view of Patton et al. (U.S. Patent No. 2003/0118510).

The rejection is respectfully traversed in view of the following remarks.

The standard for establishing a *prima facie* case of obviousness was provided in a previous response by Applicants.

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Patton et al. is cited for teaching the meaning of PEG, structures and architectures of PEG, terminal groups of PEG, conjugate linkages, and so forth.

Patton et al., however, does not remedy the deficiencies of Minamino et al. and Davis et al. That is, the feature of 1-mer conjugates, 2-mer conjugates or 3-mer conjugates of water-soluble polymers covalently attached to a Factor VIII moiety, wherein each water-soluble polymer has a nominal average molecular weight in the range of from 6,000 Daltons to 150,000 Daltons is neither disclosed nor suggested in by Minamino et al. and Davis et al. (both alone and in combination) and the teachings of Patton et al. fail address this deficiency.

Consequently, for the same reason provided in Section VI, the third prong of *prima facie* obviousness fails to be satisfied. As a result, the obviousness rejection of claims 1-10, 12-13, 21, 24-28 and 62 under 35 U.S.C. §103(a) is unsustainable. Reconsideration and withdrawal of the rejection for at least the reasons provided above is respectfully requested.

### **VIII. The Fifth Rejection Under 35 U.S.C. §103(a)**

The Examiner rejected claims 1, 29 and 30 under 35 U.S.C. §103(a) as allegedly being unpatentable over Minamino et al. (U.S. Patent No. 6,037,452) in view of Davis et al. (U.S. Patent No. 4,179,337) as applied to claims 1-4, 8-9, 14-15, 17-20, 22-23 and 62, and further in view of Bentley et al. (U.S. Patent No. 2003/0161791).

The rejection is respectfully traversed in view of the following remarks.

The standard for establishing a *prima facie* case of obviousness was provided in a previous response by Applicants.

Bentley et al. is cited for teaching a conjugate comprising a thioether or disulfide linkage.

Bentley et al., however, does not remedy the deficiencies of Minamino et al. and Davis et al. That is, the feature of 1-mer conjugates, 2-mer conjugates or 3-mer conjugates of water-soluble polymers covalently attached to a Factor VIII moiety, wherein each water-soluble polymer has a nominal average molecular weight in the range of from 6,000 Daltons to 150,000 Daltons is neither disclosed nor suggested in by Minamino et al. and Davis et al. (both alone and in combination) and the teachings of Bentley et al. fail address this deficiency.

Consequently, for the same reason provided in Section VI, the third prong of *prima facie* obviousness fails to be satisfied. As a result, the obviousness rejection of claims 1, 29 and 30

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under 35 U.S.C. §103(a) is unsustainable. Reconsideration and withdrawal of the rejection for at least the reasons provided above is respectfully requested.

#### IX. Conclusion

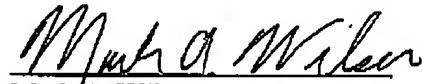
In view of the foregoing, Applicants submit that the pending claims satisfy the requirements of patentability and are therefore in condition for allowance. Reconsideration and withdrawal of all objections and rejections is respectfully requested and a prompt mailing of a Notice of Allowance is earnestly solicited.

If a telephone conference would expedite the prosecution of the subject application, the Examiner is requested to call the undersigned at (650) 620-5506.

Respectfully submitted,

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By:

  
Mark A. Wilson  
Registration No. 43,275

Nektar Therapeutics  
150 Industrial Road  
San Carlos, CA 94070  
(650) 631-3100 (Telephone)  
(650) 631-3125 (Facsimile)